

## DISSERTATION SUMMARY

Presented PhD dissertation, encompassing a series of four scientific papers, demonstrates research findings aimed at the in-depth characterization of thermal properties, internal structure, intermolecular interactions, molecular dynamics, as well as the nature of phase transitions on the example of selected hydrogen bonded active pharmaceutical ingredients (APIs) and their derivatives with different degrees of disorder (i.e., ticagrelor (TICA), enantiomers of flurbiprofen and their racemic mixture (*R*-, *S*- and *RS*-FLP), 1-adamantylamine (1-NH<sub>2</sub>-ADM), 1-adamantanol (1-OH-ADM), and 3-amino-1-adamantanol (3-NH<sub>2</sub>-1-OH-ADM)) over a wide range of temperatures and pressures. The key role was played by high-pressure broadband dielectric spectroscopy (BDS) measurements, which provided information on the atomic structure, indirectly the strength and population of hydrogen bonds, the global/local dynamics, as well as the effect of high compression on phase transitions in structurally similar systems, forming plastic crystalline (PC) phases.

Dielectric investigations carried out on TICA showed strong sensitivity of structural relaxation ( $\alpha$ ) to pressure, as well as fulfillment of the temperature-pressure superpositioning (TPS) rule, which is usually broken for highly associated systems. Based on complementary infrared (IR) studies on pressure-densified glass (PDG) and ordinary glass (OG), and comparison of the obtained results to those determined for ritonavir, it was suggested that the reason for the above-mentioned behavior is the unchanged hydrogen-bonding pattern at high compression. Moreover, it was demonstrated that under isochronal conditions, the ratio of  $\alpha$  and secondary ( $\beta$ -JG) relaxation times is constant for TICA, as well as the entropy of activation for  $\beta$ -relaxation is positive and increases with compression (probably due to small conformational changes of molecules at elevated pressure).

In turn, comprehensive studies performed on *R*-, *S*-, and *RS*-FLP indicated that these systems, in the context of molecular orientation, are completely indistinguishable after melting and in the supercooled liquid phase. However, a deeper analysis of high-pressure dielectric data showed an unexpected fluctuation in activation volume ( $\Delta V_\alpha$ ) between the pure enantiomers and their racemate (a lower value of  $\Delta V_\alpha$  was obtained for *RS*-FLP). Based on the results of molecular dynamics simulations, the observed effect was attributed to variations in the local molecular arrangement of the studied compounds, more specifically, to a higher contribution of smaller supramolecular clusters in the enantiomers. In addition, based on the outcomes of DFT calculations, the existence of specific, extremely strong F- $\pi$  bonds, which are the driving force

for the different local molecular ordering in the supercooled liquid phase, as well as the crystalline state of the examined systems, was indicated.

Meanwhile, the results of investigations conducted on adamantane (ADM) derivatives revealed the presence of phase transitions between four PC phases: PC(I)-PC(II), PC(II)-PC(III), PC(III)-PC(IV) in 1-NH<sub>2</sub>-ADM, a phase transition from the ordinary crystal (OC) to the PC phase in 1-OH-ADM, and OC-PC and PC(I)-PC(II) phase transitions in 3-NH<sub>2</sub>-1-OH-ADM. In addition, the same sequence and nature of phase transitions during both cooling and compression cycles were demonstrated for 1-NH<sub>2</sub>-ADM and 1-OH-ADM. What is also interesting, the additional isothermal, time-dependent BDS and IR experiments proved that OC-PC(I) and PC(I)-PC(II) phase transitions in 3-NH<sub>2</sub>-1-OH-ADM and 1-NH<sub>2</sub>-ADM, respectively, are physical phenomena with a character of the kinetic process.

The findings presented in this dissertation provide valuable insights into the molecular dynamics and nature of phase transitions in associated systems with different degrees of disorder. Discussed aspects such as the relationship between the variation in the population of hydrogen bonds and the shape of the  $\alpha$ -dispersion, which can be followed by studying the properties of PDG (TICA), the correlation between the internal structure, interactions, and physical properties of optical isomers and their mixture (*R*-, *S*-, and *RS*-FLP), as well as the properties of the systems forming orientationally disordered phases (ADM derivatives) make a great contribution to the discussion on amorphous APIs as well as plastic crystals.